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Opportunities for earlier diagnosis of type 1 diabetes in children: A case-control study using routinely collected primary care records

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ABSTRACT

Background: The epidemiology of type 1 diabetes mellitus (T1DM) suggests diagnostic delays may contribute to children developing diabetic ketoacidosis at diagnosis. We sought to quantify opportunities for earlier diagnosis of T1DM in primary care.

Methods: A matched case-control study of children (0–16 years) presenting to UK primary care, examining routinely collected primary care consultation types and National Institute for Health and Care Excellence (NICE) warning signs in the 13 weeks before diagnosis.

Results: Our primary analysis included 1920 new T1DM cases and 7680 controls. In the week prior to diagnosis more cases than controls had medical record entries (663, 34.5% vs 1014, 13.6%, odds ratio 3.46, 95% CI 3.07–3.89; $p < 0.0001$) and the incidence rate of face-to-face consultations was higher in cases (mean 0.32 vs 0.11, incidence rate ratio 2.90, 2.61–3.21; $p < 0.0001$). The preceding week entries were found in 330 cases and 943 controls (17.2% vs 12.3%, OR 1.49, 1.3–1.7, $p < 0.0001$), but face-to-face consultations were no different (IRR 1.08 (0.9–1.29, $p = 0.42$)).

Interpretation: There may be opportunities to reduce time to diagnosis for up to one third of cases, by up to two weeks. Diagnostic opportunities might be maximised by measures that improve access to primary care, and public awareness of T1DM.

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1. Introduction

The incidence of type-1 diabetes mellitus (T1DM), a chronic condition characterised by lack of insulin, peaks in children aged 5–7 years and in adolescents [1–4]. The UK has a comparatively high incidence of T1DM, at between 17 and 24 per 100,000 children, but even so the first presentation of a child with new-onset T1DM is an uncommon event for General Practitioners (GPs) [5].

A failure to administer insulin leads inevitably to diabetic ketoacidosis (DKA), the metabolic state characterised by the triad of hyperglycaemia, acidosis and ketonaemia, as a result harm can occur from a relatively short diagnostic delay. DKA has a mortality of 0.15–0.3% and is the leading cause of death in children with T1DM, being implicated in 83% of deaths [6,7]. Children are particularly vulnerable to DKA at the time of initial diagnosis, when 25% suffer DKA compared to 4–5% of children each year subsequently [8].

Epidemiological patterns support the hypothesis that diagnostic delay contributes to DKA at presentation [9]. Children given a diagnosis other than diabetes by their primary care doctor or whose diagnosis is delayed by as little as 24 h have a higher risk of ketoacidosis [10,11]. Children under the age of five years also have higher risk of DKA than older children [8,11]. It is possible that presenting with less obvious clinical patterns, and being less able to communicate symptoms contributes to delay. Children with infections at diagnosis are also high risk for DKA. As well as causing physiological disturbances infection might also confound the diagnostic process [8,11]. Underserved groups, for example children of ethnic minority and of lower socioeconomic status, are at higher risk of DKA at diagnosis [8,11]. Conversely, children with a first degree relative with T1DM, and children with more highly educated parents appear to be at lower risk of DKA, suggesting that access to medical care and diabetes awareness may facilitate timely diagnosis [8].

Clinical guidance issued by the UK's National Institute for Health and Care Excellence (NICE) describes alarm symptoms for T1DM (thirst, polyuria, weight loss, abdominal pain or fatigue) and symptoms of possible DKA (nausea or vomiting, hyperventilation, dehydration and reduced level of consciousness) [12]. Parents report symptoms an average of 16–17 days before diagnosis; a period long enough to potentially make an earlier diagnosis, and therefore reduce the risk of DKA [8]. NICE state that children with suspected T1DM should be referred for same day assessment by a specialist paediatric diabetes team [12]. In the UK, most unwell children are seen in primary care, but the frequency and pattern of consultations leading up to a diagnosis of T1DM is not known. We therefore sought to quantify opportunities for earlier diagnosis by examining children's primary care medical records prior to a diagnosis with T1DM, and comparing these to matched controls.

2. Methods

We conducted a case-control study of children with diabetes and matched controls, using routinely collected medical records from the 13 weeks before diagnosis. Data were provided by the THIN (The Health Improvement Network) database of routinely collected UK primary care records [13,14]. THIN presently covers the anonymised electronic medical records of 12 million patients, approximately 6% of the UK population.

Cases were aged 0–16 years and required at least one year of records prior to diagnosis (children younger than 1 year required data from birth). Cases required diabetes first coded between October 1998 and January 2011, defined by prespecified codes for a diagnosis, attending a specialist diabetes clinic, or diabetic medications. The original dataset included children with diabetes of all types. Cases with T1DM were identified by codes for the type of diabetes and for prescriptions. Cases were excluded if their records had ever been suggestive of type 2 diabetes or maturity onset diabetes of the young—either by inconsistent diagnostic codes for more than one type of diabetes, or by prescriptions [15]. Children with a consistent but unspecified diabetes type were included in the main analysis but excluded in sensitivity analyses. The index date for cases was the first date upon which the patient record indicated diabetes. These dates were then adjusted by taking into account clinical information to reduce bias due to reporting delays (Appendix A). Cases were ineligible if they had subsequent cessation of diabetic treatment or complications of diabetes without a diagnosis or if insulin had been prescribed for them more than 21 days prior to the index-date.

Cases were matched to four controls on: age, sex, registered healthcare provider, and index consultation date (controls had to have a consultation within 21 days of the index date for their matched case). Eligible controls were not diagnosed with diabetes at any point based on the same criteria as cases, and did not have any record of diabetic monitoring or possible or suspected complications of diabetes, e.g. diabetic retinopathy.

Consultation types are coded in the record, but children may have multiple codes on the same day, e.g. a code for a face-to-face visit with the GP and a code for a test and a phone call. In order to avoid double counting, the primary consultation type was determined by a hierarchical code structure (Appendix B). Because our goal was to estimate diagnostic opportunities in primary care, codes judged clinical were prioritized over those thought to be administrative, and practice-based codes were favoured over codes recording non-practice based activity. NICE alarm symptoms and DKA related outcomes were based on the presence or absence of codes suggestive of these symptoms without a hierarchical structure (Appendix C).

Matching on the index date introduced the possibility that controls were abnormally high users of healthcare (because children consulting more often have a higher probability of being selected). This was addressed in a sensitivity analysis where cases were used as their own controls, using 13 weeks preceding a consultation as close as possible to one year earlier to avoid introducing seasonal effects, and with a term for age included in the regressions to account for an extra year of life. This self-controlled analysis was undertaken on both definitions of cases (i.e. both including and excluding cases coded as diabetes of 'unspecified type').

Analyses were undertaken using Stata versions 11 and 14. Univariate associations were examined with the use of non-parametric tests (equality of median test for variables that

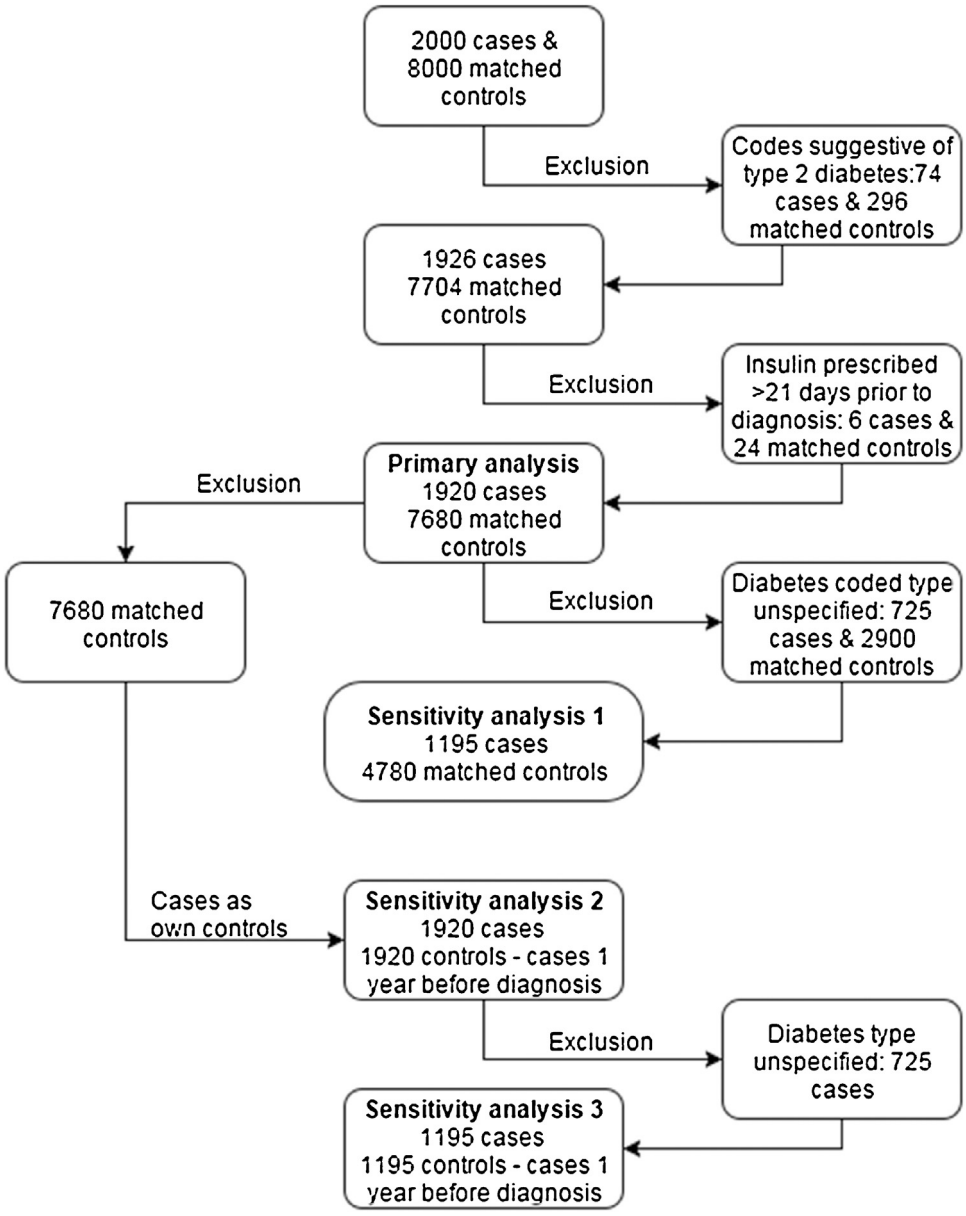

Fig. 1 – Flowchart of exclusions from analyses.

were not normally distributed) and parametric tests for normally distributed variables. We described both the number and proportion of cases and controls with record entries, and the mean and standard deviation of entries. Comparisons between cases and controls were conditioned upon clustering by matched case-control set, and were calculated with 95% confidence intervals and p values. Incidence rate ratios were calculated to compare mean consultations, using random effects Poisson regression, and odds ratios were calculated to compare the proportion of children with entries in their records using conditional logistic regression.

3. Results

Data for 2000 children with new onset diabetes and 8000 control children were extracted from the THIN database. After excluding 80 cases with a record suggestive of type 2 diabetes, 1920 cases matched to 7680 controls remained in the primary analysis. 1195 (62%) were unambiguously coded as T1DM by their practices and 725 (38%) were of unspecified type of diabetes, but had prescriptions for insulin only (Fig. 1, Table 1). During data cleaning and pre-processing the index dates of 296 (15.4%) cases were adjusted. The median adjustment was three days (IQR 2–6.5, 95th centile 14 days). For cases and controls the median age was 9.94 years and 53% were male (Table 1). In the month prior to diagnosis cases had a median of two entries in their medical records including the index date (IQR 0–2) compared to one in controls (IQR 0–1, $p < 0.001$).

In the primary analysis, cases had significantly more entries than controls for up to eight weeks prior to diagnosis, but they were only increased for the two weeks before the index date in sensitivity analyses, and we have therefore

Table 1 – Population characteristics of cases and controls.

Characteristic	Cases	Controls
Number of children	1920	7680
Age in years at index date: median (IQR)	9.94 (5.78, 13.21)	9.94 (5.78, 13.21)
Number (%) male	1026 (53.44)	4104 (53.44)
Coded Diabetes type: 1	1195	NA
Coded Diabetes type: not specified	725	NA

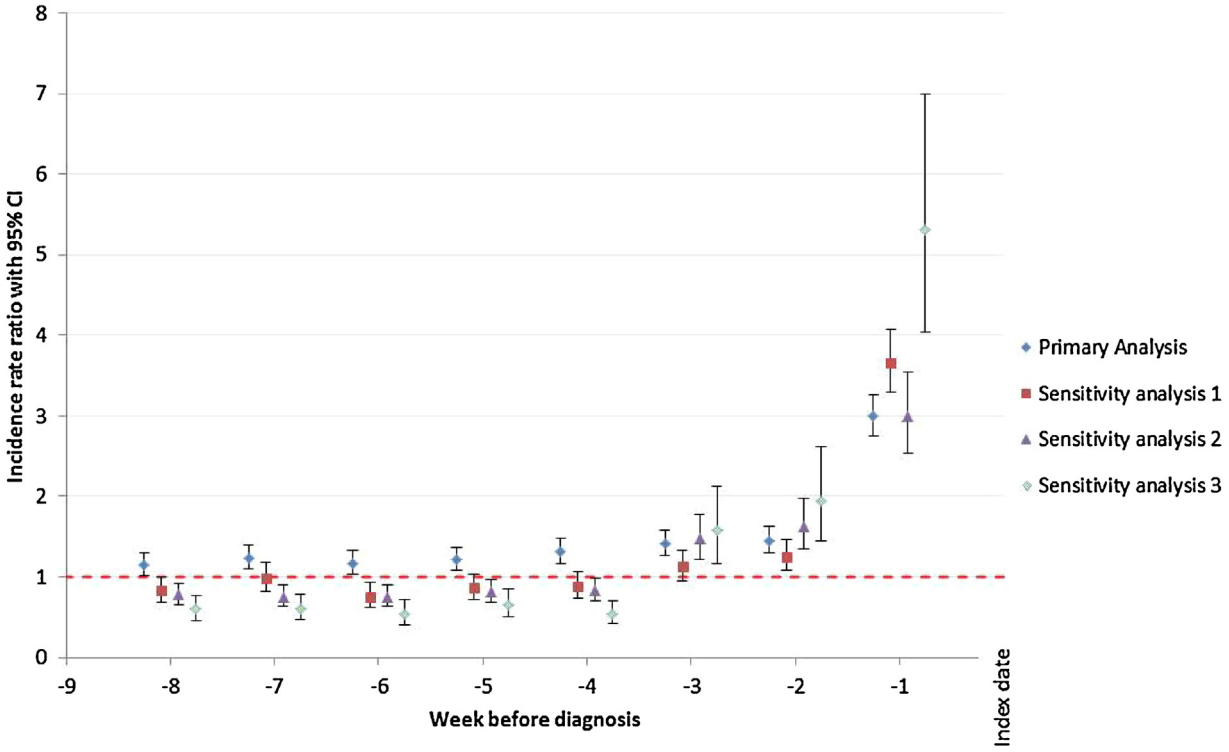

Fig. 2 – Incidence rate ratio and 95% confidence intervals for any primary care record in each week before diagnosis, comparing paediatric T1DM cases and matched controls: primary and sensitivity analyses.
Primary analysis includes 1920 paediatric T1DM cases and 7680 matched controls. Sensitivity analysis 1 excludes 725 cases with diabetes of unspecified type, leaving 1195 cases and 4780 controls. Sensitivity analysis 2 uses 1920 cases as their own self-controls. Sensitivity analysis 3 excludes the 725 cases with diabetes of unspecified type, and uses the remaining 1195 as their own self-controls.

focussed on this period (Fig. 2). Consultations began to spike in the two weeks prior to diagnosis but were highest in the week immediately prior to diagnosis (Figs. 2 and 3). During the 14 days prior to the date of diagnosis, 427 (22%) cases had records for one or more face-to-face consultations (mean 0.35, SD 0.67). Of these, 336 (17.5%) had one face-to-face consultation, 76 (4%) had two, 14 (0.7%) had three, two (0.1%) had four and one (0.05%) had five.

3.1. *At the index date*

All participants were selected by a record on the index date, but index consultations were of diverse subtypes. At diagnosis, cases interacted with their practice less than controls; 1689 cases (88%) had practice based codes compared to 7152 (93%) of controls (OR 0.52, 0.44–0.62, $p < 0.0001$) (Table 2). Face-to-face consultations were found in 43% of cases and 74% of controls (OR 0.25, 0.22–0.28, $p < 0.0001$) (Table 2, Fig. 4). Phone calls were significantly more common in cases (33% vs 9% OR 6.64 5.72–7.70, $p < 0.0001$), as were tests (Table 2).

Codes indicating one or more NICE warning signs were found in 334 cases (17.4%) and 186 controls (2.4%) (OR 8.9 7.3–10.8, $p < 0.0001$, Table 2). Codes indicating thirst were the most common, with 217 records (11%) in cases compared to 5 (0.1%) in controls (OR 174, 71.5–421, $p < 0.0001$, Table 2). At the index date abdominal pain was half as likely to be coded in cases (18, 0.9%) than controls (141, 1.8%, OR 0.5 0.31–0.83, $p = 0.007$). Codes considered potentially associated with DKA were found in ten cases (0.52%) and 18 controls (0.23%), a result of borderline significance (OR 2.3 1.03–5.00, $p = 0.041$).

3.2. *Week-1; one to seven days before diagnosis*

In week-1, 663 cases (34.5%) and 1014 controls (13.6%) had an entry in their medical record of some kind (OR 3.46, 3.07–3.89, $p < 0.0001$) (Table 3). The mean number of entries was 0.48 per

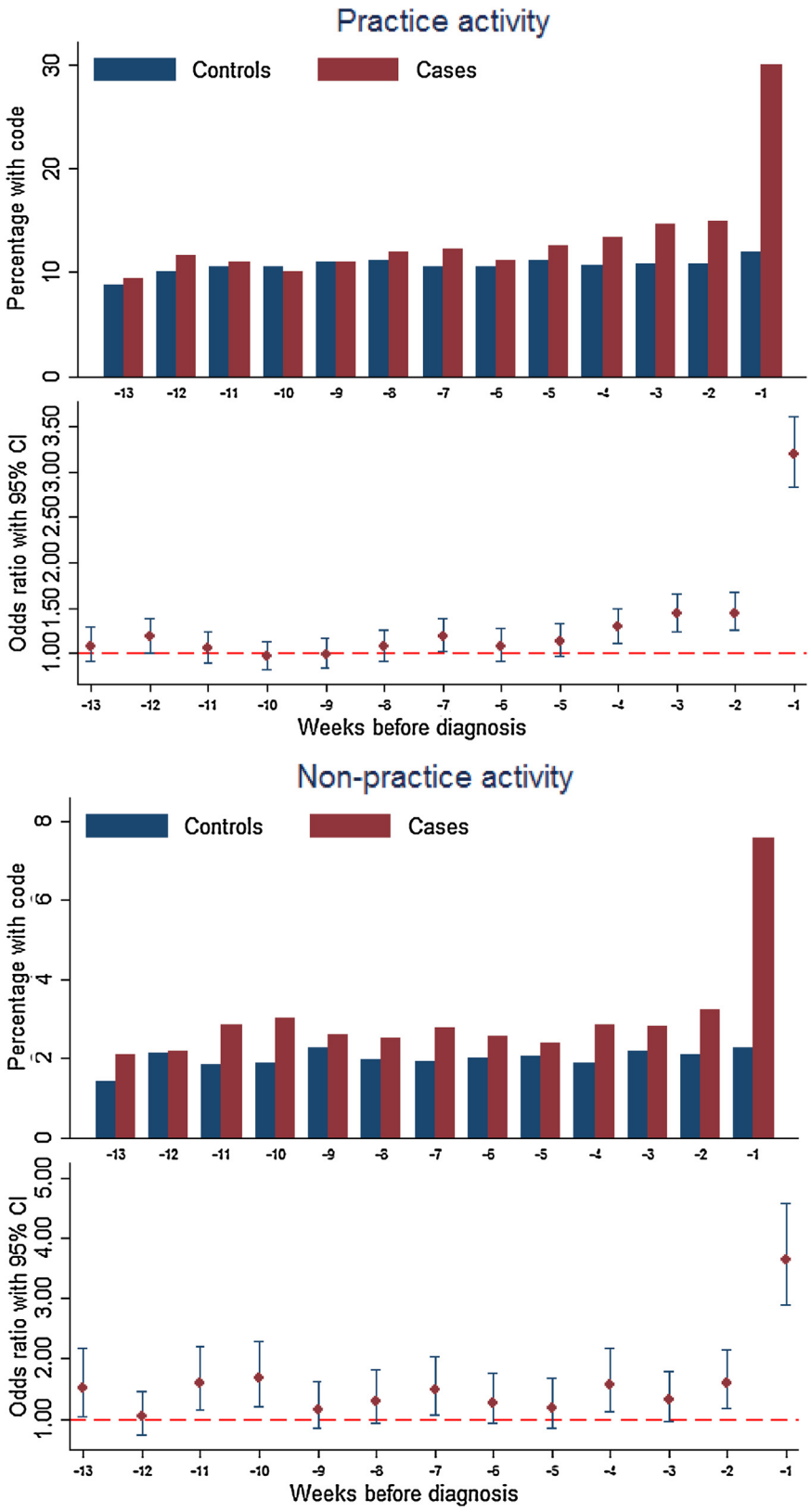

Fig. 3 – Number and odds ratios of records in cases and controls in the weeks before diagnosis—practice activity and non-practice activity.

Table 2 – The number and proportion of paediatric T1DM cases and matched controls with consultations and NICE warning signs coded in primary care medical records at the index date.

Hierarchical consultation type	Number (%)		Odds Ratio (95% CI, p)*
	Cases[a]	Controls	
All practice activity	1689 (87.97)	7146 (93.05)	0.52 (0.44–0.62)*
Practice subtypes:			
Face-to-face	825 (43.0)	5664 (73.7)	0.25 (0.22–0.28)*
Phone call	628 (32.7)	681 (8.87)	6.64 (5.72–7.70)*
Test or result	98 (5.10)	300 (3.91)	1.33 (1.05–1.68, 0.018)
Prescription	138 (7.19)	504 (6.56)	1.11 (0.91–1.35, 0.32)
All non-practice activity	231 (12.03)	531 (6.91)	1.90 (1.61–2.25)*
Non-practice subtypes:			
Admission	24 (1.25)	5 (0.07)	19.2 (7.33–50.3)*
Out-of-hours provider	7 (0.36)	76 (0.99)	0.35 (0.16–0.76, 0.009)
Other acute code	3 (0.16)	10 (0.13)	1.20 (0.33–4.36, 0.78)
Other less acute code	72 (3.75)	91 (1.18)	3.50 (2.52–4.86)*
Non-medical reports	0 (0)	0 (0)	–
Administrative	125 (6.51)	349 (4.54)	1.49 (1.20–1.84)*
Clinical contact (face-to-face or phone)	1453 (75.68)	6345 (82.6)	0.63 (0.56–0.72)*
Any record type (total)	1920 (100)	7860 (100)	–
NICE warning signs[a]			
Thirst	217 (11.3)	5 (0.07)	173.6 (71.5–421)*
Polyuria	85 (4.43)	7 (0.09)	48.6 (22.4–105)*
Weight loss	39 (2.03)	13 (0.17)	12.81 (6.70–24.5)*
Fatigue	13 (0.68)	20 (0.26)	2.6 (1.29–5.23, 0.007)
Abdominal pain	18 (0.94)	141 (1.84)	0.50 (0.31–0.83, 0.007)
Number coded per child			
0	1,586 (82.6)	7494 (97.6)	–
1	303 (15.8)	185 (2.41)	–
2	24 (1.25)	1 (0.01)	–
3	7 (0.36)	0 (0)	–
One or more	334 (17.4)	186 (2.42)	8.88 (7.28–10.83)*

* $p < 0.0001$.

[a] Case definition includes children coded with type 1 diabetes and diabetes of unspecified type. Events on the index date (day 0) are not included. Where a child had more than one type of consultation coded for a single date the type highest in the hierarchy was used. 'All practice activity' is a summation of face-to-face, phone call, tests and prescriptions. 'All non-practice activity' is a summation of admissions, out-of-hours, other acute/less acute codes, nonmedical and administrative codes. 'Clinical contact' is a summation of face-to-face and phone call consultations. The presence or absence of NICE warning signs is not hierarchical. Conditional logistic regression conditioned on matching variables only (age, sex, consultation date and practice).

case, compared to 0.16 for controls (IRR 3.00; 95% CI 2.76–3.27; $p < 0.001$) (Table 4).

Compared to controls, cases had a significantly higher incidence of both practice-based (IRR 2.88; 95% CI 2.62–3.16, $p < 0.0001$) and non-practice based activity (IRR 3.71, 3.01–4.58, $p < 0.0001$). The odds of cases having an entry in the record were significantly increased for all subtypes of practice activity. Hospital admissions were rare, with 4 admissions in cases (0.21%) compared to 2 (0.03%) in controls (OR 8.00, 1.47–43.68, $p = 0.016$).

In week-1 336 cases had face-to-face consultations; 287 (85.4%) were seen once, 45 (13.4%) twice, three (0.89%) three times and one (0.30%) had four appointments. The mean for cases was 0.2, compared to 0.08 in controls (IRR 2.42, 2.14–2.75, $p < 0.0001$). Another 178 cases (9.27%) had a telephone interaction. When face-to-face and phone-calls consultations were combined, these clinical consultations were found in 663 cases (34.5%) and 762 controls (9.92%, OR 2.96, 2.6–3.4, $p < 0.0001$) (Table 3).

In week-1 warning sign codes were recorded in 94 cases (4.9%), with the most common being for thirst, found in 48 (2.5%) cases (Table 3). Even assuming such records were made only after a face-to-face or telephone consultation with a primary care provider, one or more red flags were only coded in 18% of cases. The overall incidence of warning signs in cases was low (mean 0.008), but significantly higher than controls (IRR 10.8, 7.35–15.8; $p < 0.0001$) (Table 4). Polyuria was the warning sign most incident in cases (mean 0.03) compared to controls (mean 0.0004, IRR 66.7, 20.8–213; $p < 0.0001$) (Table 4). Abdominal pain was not statistically associated with T1DM (IRR 1.18, 0.53–2.64, $p = 0.68$).

3.3. *Week-2; eight to 14 days prior to diagnosis*

In week-2 330 (17.2%) cases had an entry in the record of some kind, compared to 943 (12.3%) controls (OR 1.49, 1.3–1.7, $p < 0.0001$) (Table 3). The mean number of entries in cases was 0.22 in week-2, compared to 0.15 in controls, with the incidence of new entries significantly higher for cases than controls (IRR 1.45 (95% CI 1.30–1.62, $p < 0.0001$)) (Table 4). The incidence of both practice-based activity (IRR 1.43; 1.27–1.62,

Table 3 – The number and proportion of paediatric T1DM cases and matched controls with consultations and NICE warning signs coded in primary care medical records in the two weeks before the index date.

Consultation hierarchy	One to seven days before diagnosis: week-1			Eight to fourteen days before diagnosis: week-2		
Consultation type	Number (%)		Odds ratio (95% CI, p)*	Number (%)		Odds ratio (95% CI, p)*
Consultation subtypes	Cases[a]	Controls		Cases[a]	Controls	
All practice activity:	576 (30.0)	921 (11.99)	3.20 (2.83–3.62)*	287 (14.9)	834 (10.86)	1.45 (1.25–1.67)*
Face-to-face	336 (17.5)	611 (8.00)	2.15 (2.12–2.83)*	137 (7.12)	523 (6.81)	1.05 (0.86–1.28, 0.6)
Phone call	178 (9.27)	187 (2.43)	4.28 (3.44–5.33)*	82 (4.27)	166 (2.16)	2.03 (1.55–2.66)*
Test or result	84 (4.38)	84 (1.01)	4.32 (3.15–5.93)*	36 (1.88)	84 (1.01)	1.74 (1.17–2.58, 0.006)
Prescription	64 (3.33)	126 (1.64)	2.06 (1.52–2.79)*	60 (3.13)	149 (1.94)	1.62 (1.20–2.20, 0.002)
All non-practice activity:	145 (7.55)	174 (2.27)	3.64 (2.89–4.59)*	62 (3.23)	161 (2.10)	1.58 (1.17–2.14, 0.003)
Admission	4 (0.21)	2 (0.03)	8.00 (1.47–43.68, 0.016)	0 (0)	1 (0.01)	–
Out-of-hours provider	14 (0.73)	18 (0.23)	3.11 (1.55–6.26, 0.001)	6 (0.31)	7 (0.09)	3.43 (1.15–10.20, 0.027)
Other acute code	4 (0.21)	3 (0.04)	5.33 (1.19–23.83, 0.028)	1 (0.05)	3 (0.04)	1.33 (0.14–12.82, 0.80)
Other less acute code	64 (3.33)	34 (0.44)	8.25 (5.34–12.75)*	22 (1.15)	41 (0.53)	2.24 (1.31–3.82, 0.003)
Non-medical reports	0 (0)	0 (0)	–	0 (0)	1 (0.01)	–
Administrative	64 (3.33)	120 (1.56)	2.26 (1.65–3.10)*	34 (1.77)	114 (1.48)	(1.20, 0.81–1.79, 0.35)
Clinical contact (Face-to-face or phone)	469 (25.8)	762 (9.92)	2.96 (2.60–3.38)*	207 (10.8)	659 (8.58)	1.29 (1.09–1.52, 0.003)
Any record type (total)	663 (34.5)	1014 (13.6)	3.46 (3.07–3.89)*	330 (17.2)	943 (12.3)	1.49 (1.30–1.71)*
NICE warning signs						
Thirst	2 (0.10)	2 (0.03)	4.00 (0.56–28.4, 0.17)	0 (0)	0 (0)	–
Polyuria	48 (2.5)	3 (0.04)	64.00 (19.93–205)*	5 (0.26)	1 (0.01)	20.00 (2.34–171, 0.006)
Weight loss	22 (1.15)	2 (0.03)	44 (10.35–187)*	1 (0.05)	6 (0.08)	0.65 (0.07–5.72, 0.70)
Fatigue	16 (0.83)	3 (0.04)	21.33 (6.22–73.2)*	1 (0.05)	4 (0.05)	1.00 (0.11–8.95, 1.00)
Abdominal pain	7 (0.36)	26 (0.34)	1.08 (0.47–2.48, 0.86)	3 (0.16)	23 (0.30)	0.52 (0.15–1.73, 0.28)
One or more	93 (4.84)	36 (0.47)	10.57 (7.16–15.59)*	10 (0.52)	29 (0.38)	1.39 (0.67–2.89, 0.37)

* $p < 0.0001$.

[a] Case definition includes children coded with type 1 diabetes and diabetes of unspecified type. Events on the index date (day 0) are not included. Where a child had more than one type of consultation coded for a single date the type highest in the hierarchy was used. 'All practice activity' is a summation of face-to-face, phone call, tests and prescriptions. 'All non-practice activity' is a summation of admissions, out-of-hours, other acute/less acute codes, nonmedicaland administrative codes. 'Clinical contact' is a summation of face-to-face and phone call consultations. The presence or absence of NICE warning signs is not hierarchical. Conditional logistic regression conditioned on matching variables only (age, sex, consultation date and practice).

Table 4 – Mean number of consultations and NICE warning signs coded in the primary care medical records of 1920 paediatric T1DM cases and 7680 matched controls, in the two weeks before diagnosis.

Consultation hierarchy	One to seven days before diagnosis: week-1			Eight to fourteen days before diagnosis: week-2		
Consultation type	Mean (SD)		Incidence rate ratio (95% CI, p)*	Mean (SD)		Incidence rate ratio (95% CI, p)*
Consultation subtypes	Cases[a]	Controls		Cases[a]	Controls	
All practice activity:	0.40 (0.69)	0.14 (0.40)	2.88 (2.62–3.16)*	0.19 (0.48)	0.13 (0.40)	1.43 (1.27–1.62)*
Face-to-face	0.20 (0.47)	0.08 (0.29)	2.42 (2.14–2.75)*	0.08 (0.30)	0.07 (0.29)	1.08 (0.9–1.29, 0.42)
Phone call	0.11 (0.38)	0.03 (0.17)	4.45 (3.67–5.40)*	0.05 (0.25)	0.02 (0.17)	2.12 (1.66–2.72)*
Test or result	0.05 (0.22)	0.01 (0.11)	4.00 (2.98–5.37)*	0.02 (0.14)	0.01 (0.11)	1.70 (1.16–2.50, 0.007)
Prescription	0.03 (0.19)	0.02 (0.13)	2.02 (1.50–2.71)*	0.04 (0.21)	0.02 (0.15)	1.78 (1.35–2.36)*
All non-practice activity:	0.09 (0.32)	0.02 (0.16)	3.71 (3.01–4.58)*	0.04 (0.21)	0.02 (0.16)	1.57 (1.19–2.08, 0.002)
Admission	0.002 (0.06)	0.0002 (0.02)	10.00 (1.94–51.54, 0.006)	0 (0)	0.0001 (0.01)	NA
Out-of-hours provider	0.007 (0.09)	0.002 (0.05)	2.95 (1.48–5.88, 0.002)	0.003 (0.06)	0.0009 (0.03)	3.43 (1.15–10.20, 0.03)
Other acute code	0.002 (0.05)	0.0004 (0.02)	5.33 (1.19–23.83, 0.028)	0.001 (0.05)	0.0004 (0.02)	2.67 (0.45–16.0, 0.28)
Other less acute code	0.04 (0.23)	0.005 (0.07)	8.80 (5.90–13.12)*	0.14 (0.14)	0.005 (0.08)	2.48 (1.52–4.04, 0.0003)
Non-medical reports	0 (0)	0 (0)	NA	0 (0)	0.0001 (0.01)	NA
Administrative	0.04 (0.20)	0.016 (0.13)	2.23 (1.66–3.00)*	0.02 (0.13)	0.15 (0.13)	1.14 (0.78–1.67, 0.49)
Clinical contact (Face-to-face or phone)	0.32 (0.62)	0.11 (0.35)	2.90 (2.61–3.21)*	0.13 (0.40)	0.10 (0.34)	1.33 (1.15–1.53)*
Any record type (total)	0.48 (0.77)	0.16 (0.44)	3.00 (2.76–3.27)*	0.22 (0.54)	0.15 (0.44)	1.45 (1.30–1.62)*
NICE warning signs						
Thirst	0.001 (0.03)	0.003 (0.02)	4.00 (0.56–28.4, 0.17)	0 (0)	0 (0)	NA
Polyuria	0.03 (0.17)	0.0004 (0.02)	66.7 (20.8–213)*	0.003 (0.05)	0.0001 (0.01)	13.2 (2.15–81.7, 0.005)
Weight loss	0.01 (0.11)	0.0003 (0.02)	29.7 (8.83–99.7)*	0.0005 (0.02)	0.0008 (0.03)	0.67 (0.08–5.54, 0.71)
Fatigue	0.009 (0.10)	0.0004 (0.02)	22.7 (6.64–77.3)*	0.0005 (0.02)	0.0005 (0.02)	0.72 (0.09–5.96, 0.76)
Abdominal pain	0.004 (0.06)	0.003 (0.06)	1.18 (0.53–2.64, 0.68)	0.002 (0.04)	0.004 (0.07)	0.43 (0.13–1.41, 0.16)
One or more	0.05 (0.23)	0.005 (0.07)	10.8 (7.35–15.8)*	0.005 (0.72)	0.005 (0.09)	1.08 (0.54–2.17, 0.83)

* $p < 0.0001$.

[a] Case definition includes children coded with type 1 diabetes and diabetes of unspecified type. Records from the index date (day 0) are not included. Where a child had more than one type of consultation coded for a single date the type highest in the hierarchy was used. 'All practice activity' is a summation of face-to-face, phone call, tests and prescriptions. 'All non-practice activity' is a summation of admissions, out-of-hours, other acute/less acute codes, nonmedical and administrative codes. 'Clinical contact' is a summation of face-to-face and phone call consultations. The presence or absence of NICE warning signs is not hierarchical. Poisson regression conditioned on matching variables only (age, sex, consultation date and practice).

p < 0.001) and non-practice based activity (IRR 1.57, 1.19–2.08; p = 0.002) was higher in cases than controls (Table 4, Fig. 3).

Only 207 cases (10.8%) had a clinical contact with their practice in week-2, of whom 137 (7.1%) were seen face-to-face (16 were seen twice). Another 82 cases (4.3%) had a telephone interaction. Face-to-face consultations were not significantly different between cases and controls (IRR 1.08, 0.9–1.29, p = 0.42), and neither were admissions, other acute codes, non-medical reports or administrative codes (Table 4).

In week-2 warning signs were infrequently coded. Only 10 cases (0.5%) had an entry for one or more NICE red flags (Table 3) and no children had an entry suggestive of DKA. The odds of a cases having a NICE warning sign coded was no higher than controls (OR 1.39, 0.67–2.89, p = 0.37) and the

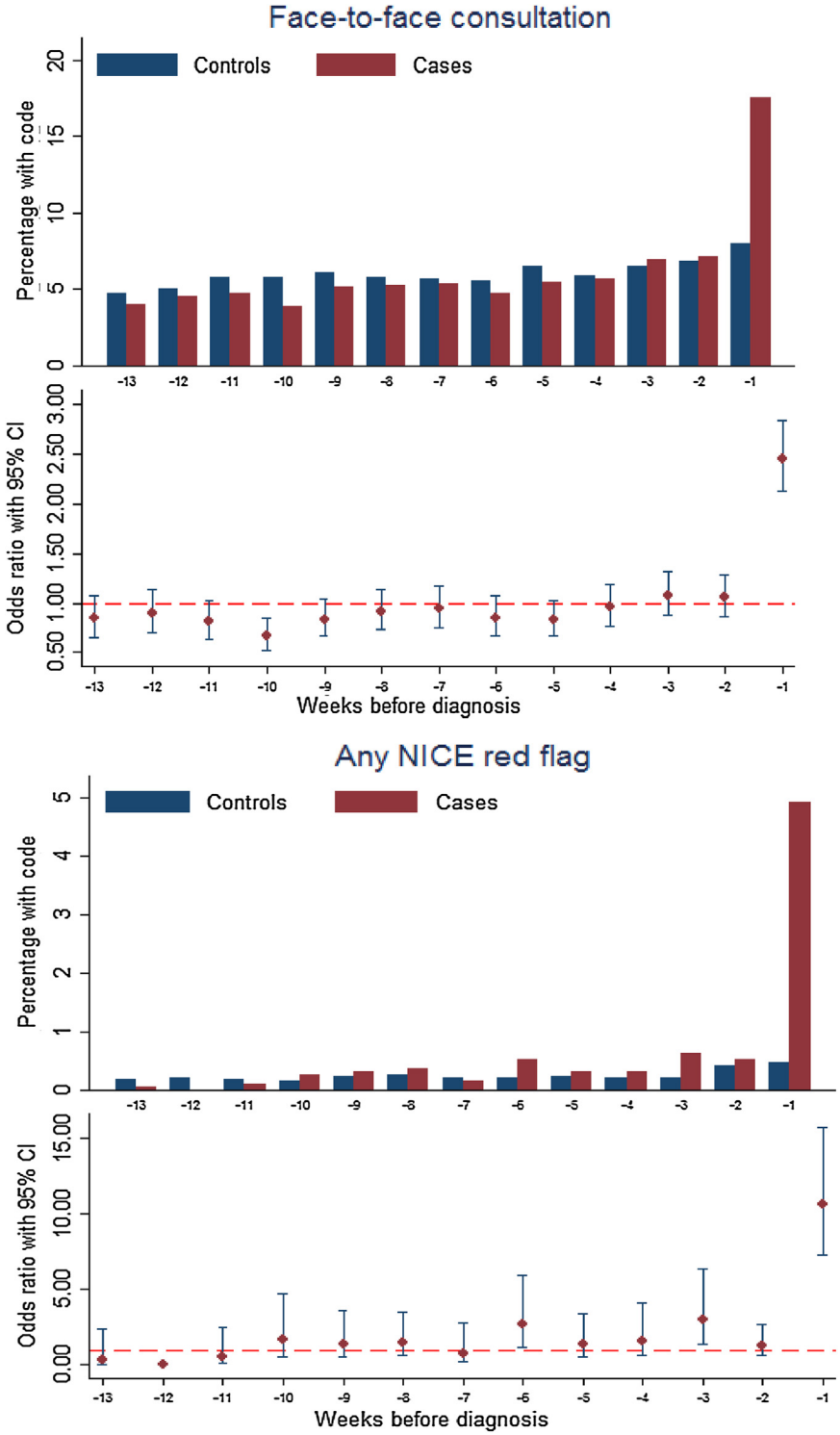

Fig. 4 – Number and odds ratios of face-to-face and NICE warning sign records in cases and controls in the weeks before diagnosis.

incidence was no higher either (IRR 1.08, 0.54–2.17, p = 0.83, Tables 3 and 4). The one warning sign that demonstrated a difference was polyuria, but this was found in only five cases (0.26%, OR 20.0, 2.34–171, p = 0.006, IRR 13.2, 2.15–81.7, p = 0.005).

3.4. *Sensitivity analyses*

In the first sensitivity analysis, 1195 unambiguously coded cases were used (excluding 725 cases with diabetes of unspecified type and their 2900 matched controls) (Fig. 1). In this analysis cases had a higher incidence of entries in the record than controls for two weeks before diagnosis. The estimated incidence rate ratio in week-1 was 3.66 (95% CI 3.29–4.08) (Fig. 2).

In the second sensitivity analysis, data from the original 1920 cases were used as their own 1:1 controls (Fig. 1). Using these self-controls, cases had significantly higher incidence of recorded entries for three weeks before diagnosis (Fig. 2).

Sensitivity analysis 3 used 1195 unambiguously coded cases, and self-controls (Fig. 1). The incidence of new entries was significantly higher in cases for the three weeks before diagnosis and five times higher in the week-1 than a year before (Fig. 2).

4. Discussion

Our study describes potential opportunities for earlier diagnosis of type 1 diabetes mellitus (T1DM) in children in UK primary care based on the pattern of primary care consultations and symptoms recorded. We found an increased number of consultations and a greater number of red flag symptoms for T1DM in the two weeks prior to diagnosis, with most occurring in the final week before diagnosis. Indeed, healthcare interactions occurred approximately three times more often in children with T1DM than controls in the week prior to diagnosis, and 1.5 times more often the week before that.

However despite these significant increases in recorded activity leading up to diagnosis, the clinical opportunities for early diagnosis in primary care are more constrained. 65% of cases have no entry in the primary care record of any kind in the week before diagnosis. Face-to-face consultations are the clearest clinical opportunities for diagnosis, but only 22% of cases were seen in the two weeks before diagnosis, and 17.5% in the final week. Given these constraints it is important to take diagnostic opportunities when they arise, as there may not be another chance. Our findings support results from a survey of 88 children with T1DM which found one in five were not diagnosed at first presentation to primary care, suggesting there may be missed diagnostic opportunities [9].

NICE recommends clinicians be aware of red flag symptoms [16]. However, very few children in this study had a coded record of these, in contrast to a survey of parents, which found a far higher proportion of children with red flag symptoms, with at least one found in all respondents; polydipsia was the most common (97.7%), followed by polyuria (83.9%), fatigue (75.9%), and weight loss (64.4%) [9]. Even at diagnosis, only 17% of children in our study had a red flag symptom coded, which may be related to a combination of difficulties recognising symptoms prospectively, or a lack of recording. Examining un-coded free text in clinical records may provide more data on symptom occurrence prior to diagnosis. Nevertheless, the classic alarm symptoms did appear to be highly specific, and therefore it is important that clinicians act when they are present. The presence of one red flag should prompt clinicians to ask about others and consider T1DM.

Our DKA related codes were rarely found in this study, despite using codes to capture unwell children, as well as those specifically coded with DKA. This contrasts with previous studies, where the rate of DKA at diagnosis was approximately 25% [11,17,18]. One explanation for this difference is that the diagnosis of DKA requires biochemical tests that are not available to most GPs, and also that these studies used hospital populations, which we would expect to be enriched for DKA because the sickest children are most likely to bypass primary care. Our low prevalence of DKA-related codes is therefore unlikely to be reflective of the overall burden of DKA at diagnosis. Future studies should consider linking primary care data to hospital records.

Examining medical codes does not allow the capture of all symptoms experienced by patients or recorded in un-coded notes by practitioners. However, our results using consultation type, which is coded automatically, should be more robust than symptom codes. The high number of 'less acute' codes such as administrative codes may represent secondary care consultations, but the clinical encounters that represent opportunities for diagnosis in primary care are unlikely to have been coded as lower priority codes. The sensitivity analyses show our incidence rate ratio estimates from the primary analysis are likely conservative, and the absolute numbers of opportunities for diagnosis are unlikely to be overestimates.

Another problem with coded data is possible recording delays, and we had to take steps to mitigate this. Doctors' strongly suspecting T1DM may only code it when the diagnosis is confirmed in secondary care, for example when a discharge letter is received following an admission to hospital. Linkage to hospital data might therefore improve the accuracy of the date of diagnosis, and would also be likely to increase the recording of DKA events. Our unlinked study may have residual recording delay if the clinician's initial diagnosis was not captured by our process, in which case the number of records prior to diagnosis and the duration of increased incidence may be artificially inflated by records of post-diagnostic diabetes care. It is therefore unlikely that we have underestimated the opportunities for earlier diagnosis.

Highlighting red flags by public health education may cause parents and caregivers to consult earlier. This could create diagnostic opportunities in primary care and reduce the incidence and severity of DKA at diagnosis. Awareness alone is unlikely to prevent all DKA at diagnosis. An intensively tested cohort of children with high genetic risk of T1DM achieved diagnoses in 36% of cases before the onset of symptoms, but even this cohort had some DKA at diagnosis (8%) [19].

Irrespective of the incidence rate ratios, new T1DM with DKA at presentation is a subset of a rare presentation to primary care. As a result, the absolute numbers are small, and the cost of reducing DKA through more timely diagnosis may be high. Researchers and policymakers should therefore consider interventions that may offer wider benefits.

Further research should examine both the diagnostic pathway in greater detail, including clinically applicable features of delayed diagnosis, and interventions designed to allow children to be seen by their primary care doctor without delay. Research should focus on the effects of improved access and awareness for children with known risk factors for DKA: young age, ethnic minorities, lack of health insurance, and children with parents of limited educational attainment. Measures to facilitate early presentation to primary care may reduce emergency presentations with diabetes, including ketoacidosis at presentation, and could also improve health more broadly in these underserved groups.

Conflict of interest

The authors state that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.pcd.2018.02.002.

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